REMARKS

The undersigned wishes to thank Examiners Miller and Moran for discussing the Office Action during the recent interview. Briefly, during the interview, it was discussed that certain claim amendments would be made to obviate issues under 35 U.S.C. 112. It was also discussed that if the Petricoin document was distinguished that should resolve issues under 35 U.S. 102 and 103.

Claims 112, 149, and 182 have been amended, and claims 221-224 have been added. No new matter has been added. For instance, support for the amendments and new clams appears e.g. at 21, lines 3-6 and page 31 of the application.

Claims 112-118, 120, 123-124, 137, 131-134, 137-139, 141-145 and 147-148 were rejected under 35 U.S.C. 112, first paragraph. As the rejection is understood, support for language in step (d) substep (iii) of claim 112 is questioned. The rejection is traversed.

The noted language of claim 112 is fully supported by the application as filed. For example, attention is directed to page 22, lines 8-12 of the present application.

In view thereof, reconsideration and withdrawal of the rejection are requested.

Claims 112-118, 120, 123-124, 127, 131-134, 137-139, 141-145, 147-153, 157-158, 161, 165-168, 171-173, 175-178, 180-190, 192, 196-197, 200, 204-207, 210-212, 214-217, and 219-220 were rejected under 35 U.S.C. 112, second paragraph.

While Applicants disagree with the rejection, and consider that the claims are readily understood as presented, the claims also have been amended without limitation to obviate the rejection.

Thus, claim 112 has been amended to provide further antecedent basis. Claim 112 also has been amended in steps (b) and (e) to indicate the reference is to classify. Such amendments also have been made in claim 182.

Claims 149 and 182 do not recite "relating" by amendments made herein.

Claim 182 also has been amended to provide further antecedent basis.

In view thereof, reconsideration and withdrawal of the rejection are requested.

Claims 112-117, 123-124, 127, 131-134, 137-139, 141, 143-145 and 148 were rejected under 35 U.S.C. §102(a) over Petricoin, *The Lancet*, 359:572-577 ("Petricoin").

Claim 147 was rejected under 35 U.S.C. under 35 U.S.C. §103(a) over Petricoin in view of Golub, *Science*, 286:531-537 ("Golub").

Claims 118, 120, 142, 149-153, 157-158, 161, 165-168, 171-173, 175-178, 181-190, 192, 196-197, 200, 204-207, 210-212, 214-217 and 220 were rejected under 35 U.S.C. under 35 U.S.C. §103(a) over Petricoin in view of Barnhill, U.S. Patent No. 6,789,069.

Claims 180 and 219 were rejected under 35 U.S.C. under 35 U.S.C. §103(a) over Petricoin in view of Barnhill, U.S. Patent No. 6,789,069 ("Barnhill"), and further in view of Golub, *Science*, 286:531-537 (1999).

For the sake of brevity, the four rejections are addressed in combination. Such a combined response is considered appropriate because, *inter alia*, each rejection relies on the Petricoin document as the sole or primary citation.

The rejections are each traversed.

Applicant's claims call for performing multivariate analysis on a **first set** of samples that includes samples classified into at least two different biological states (e.g., cancer and non-cancer) and, **separately**, performing multivariate analysis on a **second set** of samples that includes samples classified into the different biological states. By doing so, the method allows one to select biomarkers common to both sets, thereby providing an internal validation of biomarkers one cannot achieve by examining only a first set of samples. Therefore, the method assists in determining whether a biomarker actually reflects, e.g., the underlying disease or reflects a preanalytical bias, such as sex bias in the population, age bias, collection method bias, etc.

As the present application describes at page 2, lines 4-6, the "commonly accepted approach has been to pool data from multiple sources to form a combined data set and then to divide the data set into a discovery/training set and a test validation set."

In contrast, Applicants' independent claim 112 calls for "providing first data from a first set of samples" and "providing second data from a second set of samples" wherein the the first samples and second samples come from first and second populations that have a statistically significant difference with respect to at least one preanalytical variable.

Nowhere does Petricoin suggest such methods as Applicants claim, including where the first samples and second samples come from first and second populations that have a statistically significant difference with respect to at least one preanalytical variable.

Additionally, new claims 221-224 recite that the multivariate analysis as called for in claim 112 comprises use of a pattern recognition process, such as use of a classification model.

Such a method comprising use of such multivariate analysis is clearly not disclosed or otherwise suggested by Petricoin or any of the other cited documents.

Independent claims 149 and 182 also call for first and second independent discovery data sets.

Applicants have found their disclosed preferred methods can provide notable advantages, including accurate identification of desired biomarkers. This is discussed at page 3, first paragraph of the present application:

> The invention provides bioinformatics tools to analyze expression profiling data of samples from two or more independent sources in a way which reduces the sources of variability and biases which result in identification of false targets during the drug discovery process. In contrast to prior methods, data from multiple sources are NOT pooled together in a combined data set and then divided into a discovery-training set and a test-validation set. Instead, data from multiple sources (e.g., such as multiple different clinical trial sites) are analyzed separately and independently from the others. For each source, sufficient sample size and statistical re-sampling methods (e.g., such as bootstrap analysis) help to discover biomakers that perform well in a representative population and perform *consistently* well among different randomly selected subpopulations.

Nor does Petricoin or any of the other cited documents disclose or suggest: use of an intersection subset of data elements as Applicants disclose and claim, i.e.

"selecting an intersection subset of data elements from the first and second subsets, wherein each data element in the intersection subset is a member of both of the first and second subsets" as recited in Applicants' independent claim 112;

"a third computer readable program providing instructions for selecting an intersection subset of data elements from the initial subsets, wherein each data element in the intersection subset is a member of a majority of the initial subsets" as recited in Applicants' independent claim 149; and

"executing computer readable program code providing instructions for selecting an intersection subset of data elements from the initial subsets, wherein each data element in the intersection subset is a member of a majority of the initial subsets" as recited in Applicants' independent claim 182.

Golub fails to remedy such deficiencies of the Petricoin document. Golub merely reports that prediction strength was low from laboratories using different collection protocols, see p. 533, first column. Notably, Golub also reports that sample preparations should be standardized, thereby teaching away from Applicants' method where independent discovery data sets may be collected from different locations or from using different collection protocols. Nowhere does

Golub disclose or suggest "selecting an intersection subset of data elements from the first and second subsets" as Applicants claim.

Barnhill also does not disclose or suggest use of first and second independent discovery data sets as Applicants claim. Barnhill also does not suggest "selecting an intersection subset of data elements from the first and second subsets" as Applicants claim.

Reconsideration and withdrawal of the rejections are therefore requested.

It is believed that the application is in condition for immediate allowance, which action is earnestly solicited.

Respectfully submitted,

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